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ORIGINAL ARTICLE

Impact of EU regulatory label changes for diclofenac in people with cardiovascular disease in four countries: Interrupted time series regression analysis

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Objective: Due to cardiovascular safety concerns, the European Medicines Agency (EMA) recommended new contraindications and changes to product information for diclofenac across Europe in 2013. This study aims to measure their impact among targeted populations.

Method: Quarterly interrupted time series regression (ITS) analyses of diclofenac initiation among cohorts with contraindications (congestive cardiac failure [CHF], ischaemic heart disease [IHD], peripheral arterial disease [PAD], cerebrovascular disease [CVD]) and cautions (hypertension, hyperlipidaemia, diabetes) from Denmark, the Netherlands, England and Scotland.

Results: The regulatory action was associated with significant immediate absolute reductions in diclofenac initiation in all countries for IHD (Denmark −0.08%, 95%CI −0.13, −0.03; England −0.09%, 95%CI −0.13 to −0.06%; the Netherlands −1.84%, 95%CI −2.51 to −1.17%; Scotland −0.34%, 95%CI −0.38 to −0.30%), PAD and hyperlipidaemia, the Netherlands, England and Scotland for hypertension and diabetes, and England and Scotland for CHF and CVD. Post-intervention there was a significant negative trend in diclofenac initiation in the Netherlands for IHD (−0.12%, 95%CI −0.19 to −0.04), PAD (−0.13%, 95%CI −0.22 to −0.05), hypertension, hyperlipidaemia and diabetes, and in Scotland for CHF (−0.01%, 95%CI −0.02 to −0.007%), IHD (−0.017, 95%CI −0.02, −0.01%), PAD and hypertension. In England, diclofenac initiation rates fell less steeply. In Denmark changes were more strongly associated with the earlier EMA 2012 regulatory action.

Conclusion: Although significant reductions in diclofenac initiation occurred, patients with contraindications continued to be prescribed diclofenac, the extent of which

varied by country and target condition. Understanding reasons for such variation may help to guide the design or dissemination of future safety warnings.

KEYWORDS
cardiovascular disease, diclofenac, drug safety, epidemiology, NSAIDs, pharmacovigilance

1 | INTRODUCTION

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) widely prescribed for the management of inflammatory musculoskeletal conditions.[1] The cardiovascular risk of NSAIDs has resulted in significant regulatory attention after safety concerns emerged over the use of rofecoxib, which lead to its withdrawal.[2] Further evidence concerning the cardiovascular safety of NSAIDs later emerged, including a meta-analysis of 280 randomised controlled trials demonstrating a significantly increased risk of vascular events with use of celecoxib and diclofenac.[3]

In 2013, these cardiovascular safety concerns prompted the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) to evaluate the safety of diclofenac.[4–6] This followed a review by the EMA's Committee for Medicinal Products for Human Use (CHMP) in 2012.[7] In 2013 the EMA PRAC concluded that although diclofenac is an effective treatment for approved indications, an elevated risk of cardiovascular events occurs with systemic exposure. For the benefit-risk of diclofenac to remain favourable, new contraindications and warnings for prescribing diclofenac were recommended, along with changes to the product information and communication of these measures using a Direct Healthcare Professional Communication (DHPC) across Europe to alert prescribers to this safety information. This communication highlighted that diclofenac should be contraindicated in patients with congestive heart failure (CHF), ischemic heart disease (IHD), peripheral arterial disease (PAD) and/or cerebrovascular disease (CVD), and cautioned its use in patients with certain cardiovascular risk factors (hypertension, hyperlipidaemia and diabetes mellitus).[8] These are common cardiovascular conditions among the general population and therefore the target population is large.

Medicines regulatory actions are complex interventions and their impact can vary, particularly by geographical location.[9,10] Reasons for variation in their impact are multiple and may relate to the intended clinical indication, type of prescriber, method of dissemination, accessibility of therapeutic alternatives, perceived importance by stakeholders, type of target population and availability of downstream opportunities to change clinical guidelines.[11,12] Although the role of regulatory agencies is to alert prescribers to new safety information, the impact of such decisions on healthcare behaviour and health outcomes is challenging to measure and often poorly understood, with previous studies using heterogeneous and poor quality methods of evaluation.[12–14] We recently examined the impact of the 2013 EMA intervention on overall diclofenac prescribing, discontinuation and switching to alternative medicines in the general population.[15] We now report the impact of the 2013 EMA risk minimisation measures for diclofenac among patients specifically targeted by the intervention, namely among those with or at high risk of cardiovascular disease, across several EU countries to determine to what extent impact may have varied.

What is already known about this subject

- Diclofenac is a widely prescribed analgesic in musculoskeletal disease.
- The European Medicines Agency (EMA) recommended new contraindications and warnings for prescribing diclofenac in people with cardiovascular disease that were implemented across Europe in 2013.

What this study adds

- The EMA regulatory action was associated with significant reductions in diclofenac initiation among the target population.
- Some patients with contraindications continued to be prescribed diclofenac, the extent of which varied between country and target population.
- Further research is required to understand the reasons for the variation in impact.

2 | METHODS

2.1 | Data sources

Validated population data sources from four European countries were analysed (see Supplementary Methods for details). In brief these were:

- The Danish Register of Medicinal Products, which records all out-of-hospital prescriptions and allows linkage of drug exposures to inpatient and outpatient hospital contacts and death data.[16–18]
- The Dutch PHARMO Database Network, which contains combined data from primary and secondary healthcare settings in the Netherlands and the outpatient pharmacy database.[19]

- The United Kingdom Clinical Practice Research Datalink (CPRD), which contains primary care data. For this analysis we used only "up-to-standard" data from non-Scottish practices with the majority being from England (~90%).[20]
- The Scottish Prescribing Information System (PIS), which records all medicines dispensed from pharmacies in Scotland that can be record-linked to demographic data, Scottish Morbidity Records and death registrations for the entire population.[21]

2.2 | Study population

Target population cohorts with a history of each contraindication or caution were generated to provide aggregate time series data for analysis using a common protocol and format (EU PAS Register number EUPAS24089).[22] The availability of data from each database meant that the study start period varied by data source. For each country data were available from 2009Q1 to 2018Q1 in Denmark, 2008Q2 to 2016Q4 in the Netherlands, 2007Q1 to 2018Q1 in England and 2010Q3 to 2017Q4 in Scotland.

All patients from the target population cohorts were required to have at least one year of observation (lookback period) prior to inclusion in the cohort to allow sufficient time to determine prevalent versus incident use of diclofenac and the clinical conditions of interest. Cohort entry was defined by the latest of the date of registration with the general practice (in CPRD and PHARMO data sources) or the date of first recorded prescription or any secondary care diagnosis (in Danish and Scottish data sources) plus 1 year and the date of first diagnosis of the condition of interest. Cohort exit was defined as the first occurrence of any of the following: end of study period, end of registration with the general practice (for data from England and the Netherlands) or death (all databases). A patient was included in a time period if patients were observable for the entire quarter, ie, the first and last days of the quarter both lay between the patient's index date and their last follow-up date. Patients were allowed to appear in more than one target cohort providing they met each target cohort definition.

2.3 | Exposures

The target population cohorts consisted of patients with a diagnosis of the following contraindicated and cautioned groups (see Supplementary Methods for full definitions) therefore seven open cohorts were generated for each country. The contraindicated groups consisted of CHF, IHD, PAD and CVD. The cautioned groups consisted of hypertension, hyperlipidaemia and diabetes mellitus. Read, ICD or ICPC codes were used to classify licenced indications into osteoarthritis, acute gout (and other crystal arthropathies) and other inflammatory arthropathies. The classification was based on any record dated before the end of the time point.

2.4 | Outcome

The outcomes of interest were (a) the immediate change in diclofenac initiation in the quarter following the date of the regulatory action (prespecified as June 2013, ie, 2013Q2, when the EMA referral procedure concluded) and (b) the change in diclofenac initiation trend post-intervention compared to the baseline trend. Diclofenac initiation was defined as a prescription for diclofenac with no exposure to diclofenac in the preceding 92 days. The denominator was the number of nonusers on the first day of the time period, defined as no exposure to diclofenac in the previous 92 days. The numerator was the number of these patients initiating diclofenac in the time period. Prevalent users were therefore not included.

2.5 | Statistical analysis

Data were analysed as a series of proportions from aggregated patient counts evaluated in each quarter over the study period. Interrupted time series (ITS) regression analysis was used to fit quarterly time trends for each country (see Supplementary Methods for further details). The effect of the intervention within each target population in each country was represented either by a step function or by a continuous linear function modelling the baseline slope before the intervention time point, the change in slope from the baseline trend to the post-intervention trend and the immediate change associated with the intervention time point.[23] Before fitting all regression models, data were visualised graphically. All regression models were fitted separately in each country. The range of data points was trimmed to periods immediately before and after June 2013 where trends were approximated to be linear when discontinuities occurred. In a post hoc secondary analysis, we fitted the ITS analysis for Denmark using the step change that occurred in quarter three of 2012 coinciding with the diclofenac recommendation from the CHMP.[7] All models were checked for autocorrelation using the Durbin-Watson statistic and analysis was carried out using SAS V9.4.

2.6 | Ethical permissions

Permission to conduct the study in each database was obtained from the relevant source from each country, according to each database's standard terms and conditions (see Supplementary Methods for further details).

2.7 | Public and patient involvement

This study was endorsed by the EMAs PRAC committee, which consists of patient and healthcare professional representatives.

3 | RESULTS

Among all target populations the most common indication for diclofenac initiation was osteoarthritis. The proportion of patients initiating diclofenac at baseline with cardiovascular disease contraindications ranged from 0.6% (95%CI 0.6-0.7%) to 0.8% (95%CI 0.8-0.9%) in Denmark, 6.6% (95%CI 3.8-11.1%) to 11.7% (95%CI 6.3-20.8%) in the Netherlands, 0.2% (95%CI 0.2-0.3%) to 0.6% (95%CI 0.5-0.6%) in England and 0.1% (95%CI 0.1-0.2%) in Scotland (Table 1). Corresponding numbers for people with cautions were 1.0% (95%CI 0.9-1.0%) to 1.2% (95%CI 1.1 to 1.2%) in Denmark, 7.9% (95%CI 7.6-8.2%) to 8.4% (95%CI 7.7-8.7%) in the Netherlands, 0.6% (95%CI 0.6-0.6%) to 0.7% (95%CI 0.6-0.7%) in England and 0.1% to 0.3% in Scotland (Table 1).

3.1 | Impact on diclofenac initiation in people with CHF

The baseline trend of diclofenac initiation in patients with CHF was positive in Scotland, negative in the Netherlands and there was no trend in Denmark and England (Table 2 and Figures 1 and 2). The regulatory action was associated with a significant immediate fall in diclofenac initiation in patients with CHF in England (−0.08%, 95%CI −0.12 to −0.05) and Scotland (−0.21%, 95%CI −0.24% to −0.18%). Post-intervention, there was no significant change in trend compared to baseline except for in Scotland, where there was a change from a positive to a negative trend in diclofenac initiation (−0.011%, 95%CI −0.015% to −0.007%).

3.2 | Impact on diclofenac initiation in people with IHD

The baseline trend of diclofenac initiation in patients with IHD was positive in Scotland, negative in England and the Netherlands, and there was no trend in Denmark (Table 2 and Figures 1 and 2). The regulatory action was associated with a significant immediate fall in diclofenac initiation in patients with IHD in all countries. Post-intervention, there was a significant change to a negative trend in diclofenac initiation in patients with IHD in the Netherlands (−0.116%, 95%CI −0.193 to −0.038) and Scotland (−0.017%, 95%CI −0.022 to −0.011) compared to baseline. In England, there was a positive change in trend, causing diclofenac initiation to fall significantly less steeply, whilst in Denmark there was no significant change in trend compared to baseline.

TABLE 1 Number of patients with each condition at the beginning of each cohort used for interrupted time series regression modelling

	Denmark	The Netherlands	England[a]	Scotland
Year/quarter start	2012Q2	2008Q3	2011Q3	2010Q2
Number of patients				
Contraindicated group				
CCF	70,081	77	31,760	45,432
IHD	234,273	1,833	149,185	181,618
PAD	59,323	354	79,531	39,188
CVD	131,414	183	86,634	61,271
Cautioned group				
Hypertension	911,803	24,189	956,716	553,910
Hyperlipidaemia	622,836	13,427	612,004	531,739
Diabetes	231,610	5,467	201,204	161,399
Number of diclofenac initiators (%)				
Contraindicated group				
CCF	435 (0.6)	9 (11.7)	79 (0.2)	32 (0.1)
IHD	1,958 (0.8)	168 (9.2)	619 (0.4)	243 (0.1)
PAD	453 (0.8)	30 (8.4)	451 (0.6)	53 (0.1)
CVD	917 (0.7)	12 (6.6)	302 (0.3)	45 (0.1)
Cautioned group				
Hypertension	10,623 (1.2)	1,907 (7.9)	6,398 (0.7)	1,650 (0.3)
Hyperlipidaemia	5,977 (1.0)	1,098 (8.2)	4,150 (0.7)	1,229 (0.2)
Diabetes	2,259 (1.0)	448 (8.2)	1,187 (0.6)	421 (0.3)

[a]∼10% of patients were from Northern Ireland and Wales.

Abbreviations: Q, quarter; CCF, congestive cardiac failure; IHD, ischaemic heart disease; PAD, peripheral arterial disease; CVD, cerebrovascular disease.

TABLE 2 Interrupted time series regression analysis for diclofenac initiation by contraindicated group targeted by the regulatory intervention per country

	Slope before June 2013	Step change in the first quarter after June 2013	Slope change after June 2013
Congestive heart failure			
Denmark	−0.007 (−0.031, 0.016), *P* = 0.521	−0.051 (−0.121, 0.018), *P* = 0.137	−0.001 (−0.024, 0.023), *P* = 0.954
England[a]	−0.004 (−0.010, 0.003), *P* = 0.248	−0.084 (−0.118, −0.051), *P* <0.001	0.002 (−0.005, 0.009), *P* = 0.524
Netherlands	−0.201 (−0.321, −0.081), *P* = 0.002	−1.272 (−2.599, 0.056), *P* = 0.060	0.005 (−0.153, 0.163), *P* = 0.949
Scotland	0.008 (0.004, 0.011), *P* <0.001	−0.211 (−0.243, −0.179), *P* <0.001	−0.011 (−0.015, −0.007), *P* <0.001
Ischaemic heart disease			
Denmark	0.005 (−0.013, 0.023), *P* = 0.568	−0.078 (−0.131, −0.025), *P* = 0.007	−0.014 (−0.032, 0.004), *P* = 0.118
England[a]	−0.015 (−0.022, −0.008), *P* <0.001	−0.094 (−0.132, −0.056), *P* <0.001	0.011 (0.004, 0.019), *P* = 0.006
Netherlands	−0.077 (−0.128, −0.026), *P* = 0.005	−1.838 (−2.508, −1.168), *P* <0.001	−0.116 (−0.193, −0.038), *P* = 0.005
Scotland	0.012 (0.007, 0.016), *P* <0.001	−0.339 (−0.381, −0.297), *P* <0.001	−0.017 (−0.022, −0.011), *P* <0.001
Peripheral arterial disease			
Denmark	0.012 (−0.018, 0.043), *P* = 0.396	−0.097 (−0.186, −0.008), *P* = 0.034	−0.024 (−0.055, 0.006), *P* = 0.111
England[a]	−0.023 (−0.032, −0.015), *P* <0.001	−0.093 (−0.135, −0.050), *P* <0.001	0.017 (0.008, 0.025), *P* <0.001
Netherlands	−0.057 (−0.124, 0.010), *P* = 0.093	−2.023 (−2.676, −1.371), *P* <.001	−0.130 (−0.216, −0.045), *P* = 0.004
Scotland	0.011 (0.005, 0.016), *P* <0.001	−0.257 (−0.306, −0.208), *P* <0.001	−0.016 (−0.022, −0.010), *P* <0.001
Cerebrovascular disease			
Denmark	0.013 (−0.022, 0.047), *P* = 0.440	−0.073 (−0.174, 0.028), *P* = 0.143	−0.025 (−0.060, 0.010), *P* = 0.143
England[a]	−0.013 (−0.019, −0.007), *P* <0.001	−0.073 (−0.103, −0.043), *P* <0.001	0.009 (0.003, 0.015), *P* = 0.006
Netherlands	−0.089 (−0.167, −0.010), *P* = 0.028	−1.878 (−2.781, −0.975), *P* <0.001	−0.074 (−0.181, 0.033), *P* = 0.168
Scotland	0.012 (0.008, 0.015), *P* <0.001	−0.235 (−0.264, −0.206), *P* <0.001	−0.015 (−0.019, −0.011), *P* <0.001

[a]∼10% of patients were from Northern Ireland and Wales.
Trends in diclofenac initiation rates are percentages per quarter.

3.3 | Impact on diclofenac initiation in people with PAD

The baseline trend of diclofenac initiation in patients with PAD was positive in Scotland, negative in England and there was no trend in the Netherlands and Denmark (Table 2 and Figures 1 and 2). The regulatory action was associated with a significant immediate fall in diclofenac initiation in patients with PAD in all countries. Post-intervention, there was a significant change to a negative trend in diclofenac initiation in patients with PAD in the Netherlands (−0.130%, 95%CI −0.216 to −0.045) and Scotland (−0.016%, 95%CI −0.022 to −0.010) compared to baseline. In England, there was a positive change in trend, causing diclofenac initiation to fall significantly less steeply, and in Denmark there was no significant change in trend.

3.4 | Impact on diclofenac initiation in people with CVD

The baseline trend of diclofenac initiation in patients with CVD was positive in Scotland, negative in England and the Netherlands, and there was no trend in Denmark (Table 2 and Figures 1 and 2). The regulatory action was associated with a significant immediate fall in diclofenac initiation in patients with CVD in the Netherlands (−1.88%, 95%CI −2.78 to −0.98), England (−0.073%, 95%CI −0.103 to −0.043)

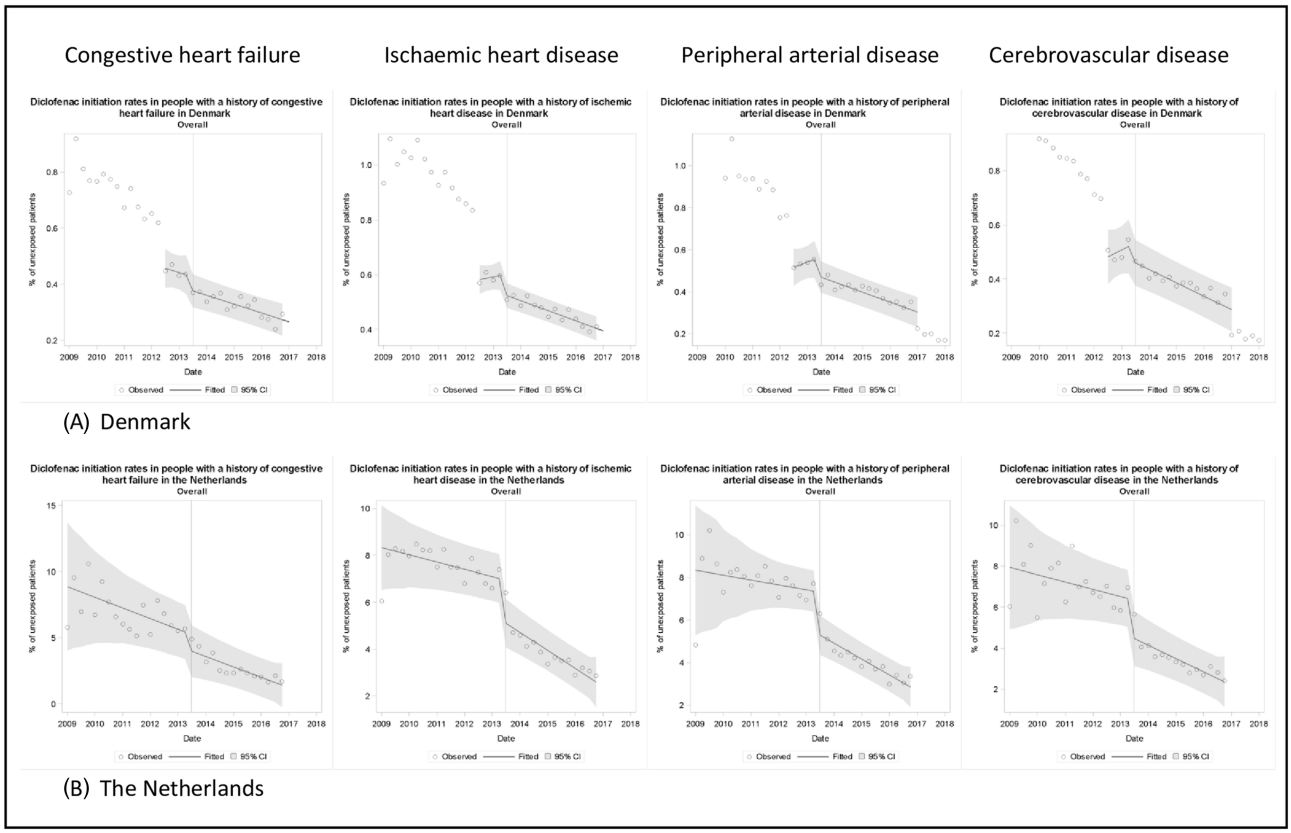

FIGURE 1 Diclofenac initiation rates in patients with new contraindications following the 2013 EMA regulatory action in (A) Denmark and (B) the Netherlands

and Scotland (−0.235%, 95%CI −0.264 to −0.206), but not in Denmark. Post-intervention, there was a significant change to a negative trend in diclofenac initiation in patients with CVD in Scotland (−0.015%, 95%CI −0.019 to −0.011) compared to baseline. In England, there was a positive change in trend, causing diclofenac initiation to fall significantly less steeply, and in the Netherlands and Denmark there was no significant change in trend.

3.5 | Impact on diclofenac initiation in people with hypertension

The baseline trend of diclofenac initiation in patients with hypertension was negative in England and there was no trend in Denmark, Scotland and the Netherlands (Table 3 and Figures 3 and 4). The regulatory action was associated with a significant immediate fall in diclofenac initiation in patients with hypertension in all countries apart from in Denmark. Post-intervention, there was a significant change to a negative trend in diclofenac initiation in patients with hypertension in the Netherlands (−0.121%, 95%CI −0.202 to −0.040) and Scotland (−0.028%, 95%CI −0.046 to −0.010) compared to baseline. In England, there was a positive change in trend, causing diclofenac initiation to fall significantly less steeply, and in Denmark there was no significant change in trend.

3.6 | Impact on diclofenac initiation in people with hyperlipidaemia

The baseline trend of diclofenac initiation in patients with hyperlipidaemia was falling in England and Scotland and there was no trend in Denmark and the Netherlands (Table 3 and Figures 3 and 4). The regulatory action was associated with a significant immediate fall in diclofenac initiation in patients with hyperlipidaemia in all countries. Post-intervention, there was a significant change to a negative trend in diclofenac initiation in the Netherlands (−0.143%, 95%CI −0.222 to −0.063) compared to baseline. Post-intervention, there was a positive change in trend in diclofenac initiation in England, causing it fall significantly less steeply, while in Denmark and Scotland there was no significant change in trend.

3.7 | Impact on diclofenac initiation in people with diabetes

The baseline trend of diclofenac initiation in patients with diabetes was negative in England and Scotland compared to in Denmark and the Netherlands, where it was flat (Table 3 and Figures 3 and 4). The regulatory action was associated with a significant immediate fall in diclofenac initiation in patients with diabetes in all countries except

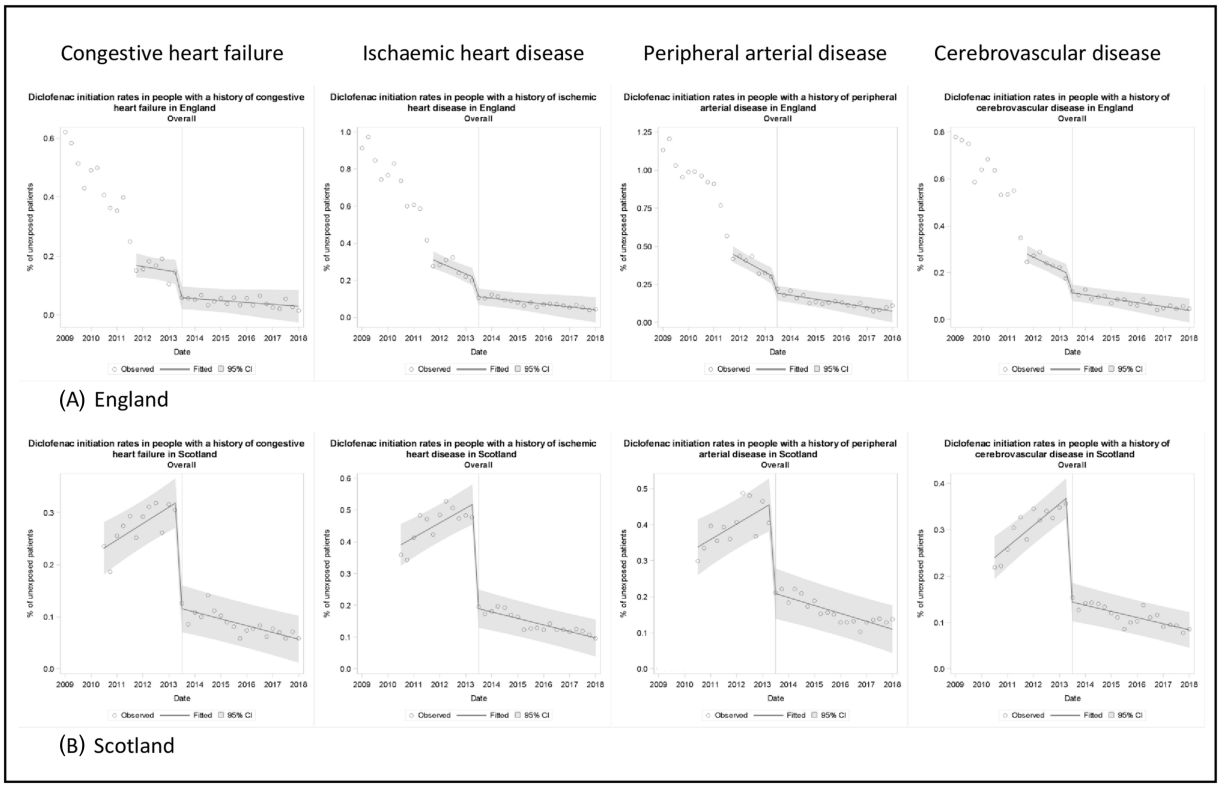

FIGURE 2 Diclofenac initiation rates in patients with new contraindications following the 2013 EMA regulatory action in (A) England and (B) Scotland

Denmark. Post-intervention, there was a significant change to a negative trend in diclofenac initiation in the Netherlands (−0.131%, 95%CI −0.221 to −0.041) compared to baseline, while in England there was a positive change in the trend, causing diclofenac initiation to fall less steeply, while in Denmark and Scotland there was no significant change in trend.

3.8 | Secondary analysis

The step change occurring in 2012Q3 in Denmark coinciding with the CHMP review was associated with a significant immediate fall in diclofenac initiation among all contraindicated and cautioned groups, and significant slowing in the negative baseline trend in diclofenac initiation (Supporting Information Table S1 and Figure S1).

4 | DISCUSSION

The 2013 EMA regulatory action focusing on the cardiovascular safety of systemic diclofenac products had a significant impact on diclofenac initiation among patients with target cardiovascular disease contraindications and cautions, the magnitude and type of which varied between countries. In patients with IHD, PAD and hyperlipidaemia, diclofenac initiation immediately fell in all countries. However, the impact on longer-term prescribing in patients with or at high risk of cardiovascular disease was more variable. The Netherlands had the highest prevalence of diclofenac prescribing. In Scotland, significant reductions in diclofenac initiation occurred in all target populations apart from in patients with hyperlipidaemia and diabetes, whilst in England longer-term changes were associated with a slowing in an already falling rate. In Denmark, small immediate falls in diclofenac initiation were observed in patients with IHD, PAD and hyperlipidaemia only, without any significant changes in longer-term prescribing, suggesting that the 2013 EMA referral procedure may have had a limited impact in Denmark.

We observed similar changes in target populations as among the population as a whole, but percentile changes tended to be larger. For example, the regulatory action was associated with a −0.42% significant immediate step reduction in diclofenac initiation in the Netherlands among the overall population compared to −1.3%, −1.8%, −2.0% and −1.9% among those with CHF, IHD, PAD and CVD, respectively.[15] A similar effect was seen with significant changes in post-intervention trend and suggests that the effect of the regulatory action was more concentrated among the target populations.

Limited impact of the EMA regulatory action has been noted in Lithuania, where diclofenac prescribing remained unchanged.[24] Geographical variation in impact is not new and has been associated with other types of regulatory procedures.[10] Variation in impact may relate to cultural differences in prescribing and pharmacovigilance practices between countries, for example whether diclofenac is prescribed short term or long term, and the clinical indication.[25,26] In our

TABLE 3 Interrupted time series regression analysis for diclofenac initiation by cautioned group targeted by the regulatory intervention per country

	Slope before June 2013	Step change in first quarter after June 2013	Slope change after June 2013
Hypertension			
Denmark	0.013 (−0.029, 0.056), P = 0.509	−0.116 (−0.239, 0.008), P = 0.065	−0.033 (−0.075, 0.010), P = 0.123
England[a]	−0.023 (−0.028, −0.018), P = <0.001	−0.134 (−0.160, −0.107), P = <0.001	0.016 (0.010, 0.021), P = <0.001
Netherlands	−0.016 (−0.065, 0.033), P = 0.513	−1.491 (−2.198, −0.785), P = <0.001	−0.121 (−0.202, −0.040), P = 0.005
Scotland	−0.004 (−0.020, 0.013), P = 0.648	−1.051 (−1.194, −0.908), P = <0.001	−0.028 (−0.046, −0.010), P = 0.004
Hyperlipidaemia			
Denmark	0.016 (−0.021, 0.052), P = 0.369	−0.108 (−0.214, −0.001), P = 0.048	−0.031 (−0.068, 0.006), P = 0.091
England[a]	−0.026 (−0.032, −0.020), P = <0.001	−0.125 (−0.155, −0.094), P = <0.001	0.018 (0.012, 0.025), P = <0.001
Netherlands	−0.016 (−0.066, 0.033), P = 0.506	−1.550 (−2.242, −0.859), P = <0.001	−0.143 (−0.222, −0.063), P = <0.001
Scotland	−0.022 (−0.032, −0.011), P = <0.001	−0.704 (−0.798, −0.610), P = <0.001	0.002 (−0.010, 0.013), P = 0.791
Diabetes			
Denmark	0.011 (−0.033, 0.055), P = 0.597	−0.077 (−0.206, 0.052), P = 0.223	−0.026 (−0.071, 0.018), P = 0.228
England[a]	−0.024 (−0.031, −0.017), P = <0.001	−0.101 (−0.136, −0.066), P = <0.001	0.017 (0.010, 0.025), P = <0.001
Netherlands	−0.028 (−0.083, 0.027), P = 0.312	−1.488 (−2.275, −0.701), P = <0.001	−0.131 (−0.221, −0.041), P = 0.006
Scotland	−0.020 (−0.030, −0.010), P = <0.001	−0.668 (−0.754, −0.582), P = <0.001	0.000 (−0.011, 0.011), P = 0.997

[a]∼10% of patients were from Northern Ireland and Wales.
Trends in diclofenac initiation rates are percentages per quarter.

population, osteoarthritis was the most common indication, suggesting it was potentially used longer term, conferring a larger risk. In absolute terms, diclofenac initiation was greater in the Netherlands compared to Denmark, where other NSAIDs have been preferentially prescribed.[27] Given that numerous NSAID products exist, it is unlikely that lack of availability of therapeutic alternatives would explain such differences.

Safety communications need to reach their target audience to be effective, therefore differences in the effectiveness of communication and dissemination strategies may impact on healthcare professional awareness.[12,28] When a decision is taken to communicate information using a DHPC as part of the EMA referral, there is an obligation for the DHPC to be disseminated among all member states although the actual timing of this may not be the same. The effectiveness of this dissemination is often unknown but differences in how many healthcare professionals receive the DHPC is one potential explanation for some of this variation. Diclofenac is also commonly prescribed by general practitioners, who might be more aware of such safety issues than specialists.[11,29] For example, evidence suggests that cardiologists are much more likely to be aware of safety issues regarding medicines they prescribe compared to the cardiovascular safety issues related to medicines that other healthcare professionals prescribe.[11]

Our analysis is currently the largest study examining the impact of the 2013 EMA regulatory action on diclofenac initiation among patients with cardiovascular disease contraindications and cautions in Europe.[1,30,31] Historically, studies evaluating the impact of regulatory actions have been subject to methodological limitations, which has led to calls for robust methods to ensure that results are valid and informative.[32] The use of large, high-quality data sources and a common protocol and data format to standardise analysis from each data source are therefore particular strengths of this study.[11,12]

This study has several limitations. First, although over-the-counter (OTC) NSAID use was not captured, the primary objective was to assess the impact of regulatory action on healthcare professional prescribing, which is only indirectly reflected in OTC use. Diclofenac was not widely available OTC in these countries. For example, although diclofenac OTC status was revoked in the UK in 2015 in response to these ongoing safety concerns, ibuprofen was the much more commonly available OTC NSAID used.[33] Diclofenac is only available OTC in the Netherlands as a low-strength product and no specific changes in this status have occurred over this time, whilst diclofenac has not been available OTC in Denmark.[34] Second, ITS analysis requires that the date of the regulatory action be prespecified and trends may be affected by other confounding factors occurring simultaneously or at other points in time.[24] Due to such obvious changes in baseline trend that can violate linear regression model assumptions, only a small number of baseline time periods prior to the outcome of regulatory action from Denmark were included in the analysis. This may have reduced the power to detect significant changes associated with the conclusion of the 2013 EMA PRAC review.[24,35] Similarly, detecting significant changes associated with regulatory actions may be more difficult if baseline trends are already heading in the intended direction. In Denmark

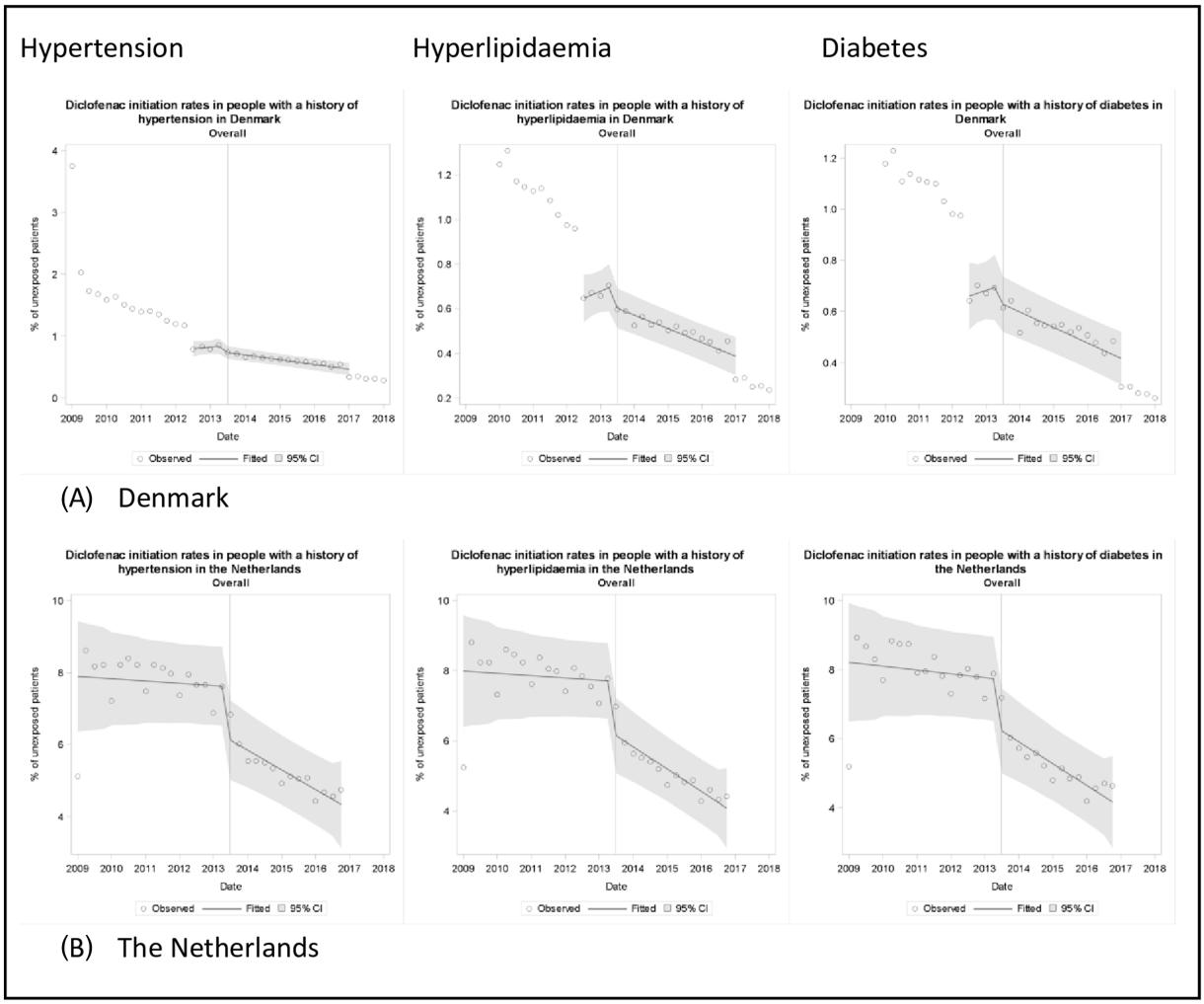

FIGURE 3 Diclofenac initiation rates in patients with new cautions following the 2013 EMA regulatory action in (A) Denmark and (B) the Netherlands

significant changes in prescribing may have occurred pre-intervention. The EMA CHMP reported potential safety concerns with NSAIDs in September 2012 that led to the PRAC safety review.[7] In post hoc analysis, when the intervention date was moved in line with the CHMP procedure in Denmark, significant immediate falls in diclofenac initiation were observed among all target populations. It is therefore possible that changes in diclofenac initiation in Denmark were influenced by regulatory action, but these changes may not have been attributable to the 2013 PRAC recommendations. It is possible that other factors may have influenced baseline trends in England, although these may have occurred before the outcome of the 2012 CHMP review.

The purpose of examining the impact of regulatory actions affecting people with or at high risk of cardiovascular disease is to determine whether regulatory action has been successful or not. This judgement is complex, however, and it is not always possible for prespecified thresholds of success to be defined. Our data suggest that although significant changes in prescribing occurred, there is perhaps room for improvement due to the fact that in all countries diclofenac initiation still occurred in some patients with known cardiovascular disease contraindications. Given the differences in prescribing rates and variation in impact, the decision as to whether further regulatory action is warranted to reinforce cardiovascular safety warnings may be better taken at national level among those countries studied. No firm recommendation can be made for member states that were not studied, where an EU-wide assessment would require better infrastructure and funding to support access and analysis of data from all EU member states.

In conclusion, the outcome of the 2013 EMA PRAC regulatory action on the cardiovascular safety of diclofenac had a significant impact on reducing diclofenac initiation among patients with cardiovascular disease contraindications and cautions, although some patients with contraindications still continue to be prescribed diclofenac in all countries. In Denmark these changes appear more strongly associated with the 2012 EMA CHMP review rather the 2013 EMA PRAC recommendations.

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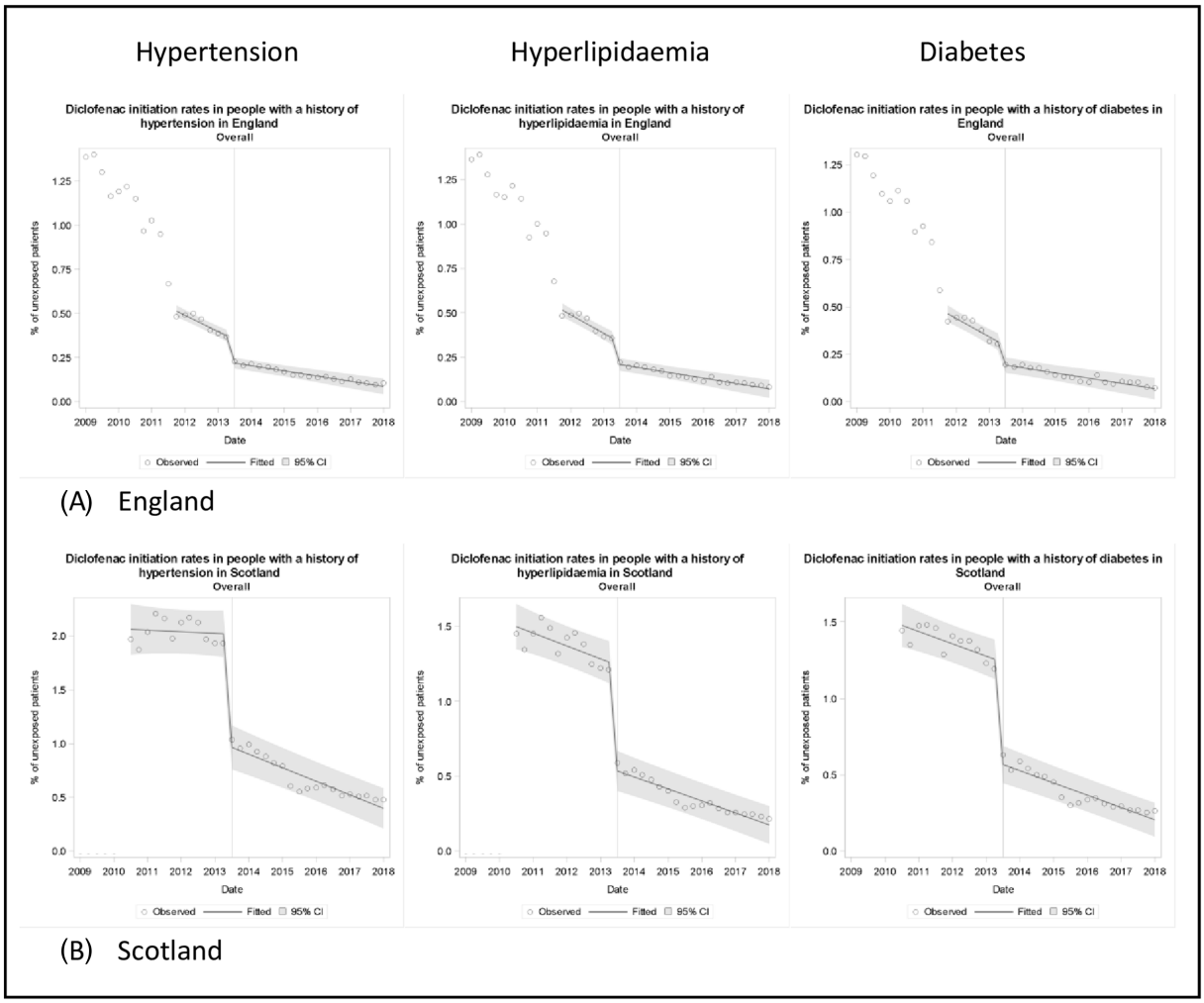

FIGURE 4 Diclofenac initiation rates in patients with new cautions following the 2013 EMA regulatory action in (A) England and (B) Scotland

general practices that contributed data to CPRD for public health purposes.

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COMPETING INTERESTS

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CONTRIBUTORS

All authors were involved in the study protocol design, project management, interpretation of results and drafting of the manuscript. S.M., L.S., M.E., C.M., L.N., D.M. and R.F. were involved in data preparation, data checking and/or data analysis. D.R.M. contributed to the study design, interpretation of results and drafted the manuscript. T.M.M. led the consortium, contributed to the protocol, the interpretation of the results and the revisions of the manuscript and is the guarantor of the study. I.S.M. and A.S.F.D. contributed to the protocol, assisted with data interpretation and reviewed the manuscript. L.M., Project managed the consortium, assisted with funding application, protocol development, coordination of analyses and revision of the manuscript. S.V.M. carried out the overall analyses and contributed to revisions of the protocol and paper. R.W.V.F. drafted the protocol and significantly contributed to all aspects of the study. J.H., M.T.E. and A.P. contributed to the protocol, sourced and ran analyses of data from Denmark assisted with data interpretation and reviewed the manuscript. R.M.C.H., E.S. and J.O. contributed to the protocol, sourced and ran analyses on data from the PHARMO database in the

Netherlands assisted with data interpretation and reviewed the manuscript. M.B. and C.R. contributed to the protocol, assisted with data interpretation and reviewed the manuscript. L.W. contributed to the protocol, assisted with data interpretation and reviewed the manuscript. L.N. and C.M. contributed to the protocol, provided data from Scotland, and assisted with data interpretation and reviewed the manuscript.

DATA AVAILABILITY STATEMENT

No data are available for sharing. Data can be accessed according to each database's standard terms and conditions for conducting observational studies.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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